GIRARDI | KEESE
THOMAS V. GIRARDI, State Bar No. 36603
tgirardi@girardikeese.com
KEITH D. GRIFFIN, State Bar No. 204388
kgriffin@girardikeese.com
1126 Wilshire Boulevard
Los Angeles, California 90017
Telephone: (213) 977-0211
Facsimile: (213) 481-1554

Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA, WESTERN DIVISION

IN RE: NEXIUM (ESOMEPRAZOLE) PRODUCTS LIABILITY LITIGATION

This Document Relates to:

ALL ACTIONS

Case No. 12-ml-2404-DSF

PLAINTIFFS' MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE PLAINTIFFS' GENERAL CAUSATION EXPERT B. SONNY BAL, M.D., J.D., M.B.A.

Crtrm.: 840--Roybal

The Hon. Dale S. Fischer

TABLE OF CONTENTS

TABLE OF AUTHORITIES

FEDERAL CASES

FEDERAL RULES

OTHER AUTHORITIES

I.

INTRODUCTION

This case involves Plaintiffs' use of Nexium (Esomeprazole) and the bone-related injuries each plaintiff sustained as a result. Nexium is a part of a class of medications known as proton pump inhibitors ("PPIs"). Nexium, and other PPIs, are used to treat a myriad of conditions, including stomach ulcers and GERD (gastroesophageal reflux disease). Nexium, when taken for more than twelve (12) months, is causally associated with osteoporosis, osteopenia, and osteoporotic-related bone fractures (collectively referred to as "OP[1]"). As plaintiffs' expert, Dr. Bal has provided well-founded opinions that Nexium is causally associated with osteoporosis, osteoporotic-related bone injuries, and reduced bone mineral density ("OP")

II.

FACTUAL BACKGROUND

A. Nexium

Nexium is a prescription drug in the class of drugs known as proton-pump inhibitors ("PPIs"). Nexium was approved for use by the Food and Drug Administration ("FDA") in 2001 for the treatment a myriad of conditions, including stomach ulcers and GERD (gastroesophageal reflux disease). After approval, several epidemiological studies emerged, finding a relationship between PPI use and OP. One such study[2] found a nearly doubled risk of spine fracture when the patient

---

[1] As Defendants' motion pertains to Dr. Bal's general causation opinions only, *see infra,* for the ease of the Court, plaintiffs refer to all injuries included in Dr. Bal's opinions as "OP". However, in using such abbreviation, Plaintiffs do not summarily agree to Defendants representation of Dr. Bal's opinions and specific Nexium-related injuries to which he gives opinions.

[2] Vestergaard, et al. *Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture*, Calcif Tissue Int. 2006; 79:76-83. (Attached as Exhibit A to Declaration of Keith D. Griffin in Support of

had used PPIs within the last year. Another study found significantly increased risks of hip fracture associated with one year (or more) PPI use.[3] Several additional studies have found increased risks of fracture and other OP injuries after using Nexium or other PPIs for more than twelve months.[4] In May 2010, the Food and Drug Administration ("FDA") issued a Safety Announcement concerning the increased risk of fractures of the hip, wrist and spine when using PPIs, including Nexium. The FDA also required labeling changes for prescription and over-the-counter PPIs containing these warnings.

B. The Nexium Litigation

After the FDA Safety Announcement, Plaintiffs filed lawsuits in the Superior Court of California against AstraZeneca Pharmaceuticals, LP, AstraZeneca, LP, and McKesson Corporation (collectively "Defendants"). Defendants removed each of the cases to California federal courts under the Class Action Fairness Act of 2005 ("CAFA"). Subsequently, the Judicial Panel on Multidistrict Litigation coordinated the cases to Multidistrict Litigation No. 2404, In re: Nexium (Esomeprazole) Products Liability Litigation, assigned to the Honorable Dale S. Fischer.

At the Court's direction, on November 1, 2013 Plaintiffs designated their general causation expert, B. Sonny Bal, M.D., J.D., M.B.A. ("Dr. Bal"), in all cases

---

Plaintiffs' Opposition to Defendants' Motion to Exclude Dr. Bal ("Griffin Declaration")

[3] Yang, et al. *Long-term proton pump inhibitor therapy and risk of hip fracture*. JAMA 2006; 296:2947-53 (*see* Griffin Declaration, Exhibit B).

[4] Targownik, et al. *Use of proton pump inhibitors and risk of osteoporosis-related fractures.* CMAJ 2008; 179(4): 319-26 (*see* Griffin Declaration, Exhibit C); Corley, et al. *Proton Pump Inhibitors and Histamine-2 Receptor Antagonists are Associated with Hip Fractures among At-Risk Patients*, Gastroenterology (2009) (*see* Griffin Declaration, Exhibit D); Gray, et al. *Proton Pump Inhibitor Use, Hip Fracture, and Change in Bone Mineral Density in Postmenopausal Women*, Arch Intern Med., 2010; 170(9): 765-771 (*see* Griffin Declaration, Exhibit E); Yu, et al. *Acid-Suppressive Medications and Risk of Bone Loss and Fracture in Older Adults*, Calcif Tissue Int., 2008; 83(4); 251-259 (*see* Griffin Declaration, Exhibit F).

as their general causation expert. Plaintiffs produced his Rule 26 expert report and produced Dr. Bal for his deposition on February 19, 2014. Plaintiffs' offered the general causation testimony of Sonny Bal, M.D., J.D., M.B.A. ("Dr. Bal"). Pursuant to Federal Rules of Civil Procedure 26, Dr. Bal submitted his expert report on November 1, 2013. On February 19, 2014, Dr. Bal gave his deposition. *See* Deposition of Sonny Bal, M.D., J.D., M.B.A. ("Bal Dep."), pertinent portions attached as Exhibit G to the Griffin Declaration. Defendants' counsel spent a large portion of the deposition presenting unfounded, irrelevant, and purely hypothetical questions to Dr. Bal on matters unrelated to his opinions regarding Nexium or other PPIs. Despite Dr. Bal's numerous qualifications and experience, Defendants filed a motion to exclude his testimony (Master Dkt. No. 255). Defendants incorrectly contend that Dr. Bal's opinions do not meet the required evidentiary standards.

C. Dr. Bal's Experience and Qualifications

Dr. Bal is a medical practitioner who specializes in orthopedics, specifically hip and knee replacements. (Bal Dep.7:9-13). Dr. Bal is board certified in orthopedic surgery and is licensed to practice medicine in Missouri and California. *See* Dr. Bal Curriculum Vitae ("Dr. Bal CV"), attached as Exhibit H to the Griffin Declaration. Dr. Bal has presented over fifty (50) peer-reviewed scientific presentations and published nearly one hundred (100) peer-reviewed journal articles. *Id.* Dr. Bal routinely treats fractures at a Level-1 trauma center at the University of Missouri School of Medicine, in patients with osteoporotic, and non-osteoporotic bone, and has first-hand knowledge of the consistency, feel, biomechanical properties, physiology, and healing properties of osteoporotic bone because most patients who require hip or knee replacement surgery are of older age and of a demographic profile that suffers from varying degrees of osteoporosis. Uniquely, as an expert, Dr. Bal operates and manipulates osteoporotic, and non-osteoporotic bone regularly in his surgical practice, and therefore has close knowledge of how such bone tolerates surgical intervention, operative fixation, reconstruction, and ultimate

performance with orthopedic implants. In his clinical practice interviewing and treating patients with and without osteoporosis, Dr. Bal has intimate familiarity with osteoporosis, the variables that can contribute to the development of osteoporosis, and the treatment modalities targeted at treating osteoporosis. Dr. Bal has over 20 years of valuable clinical experience directly related to the matters he offers opinions on in this litigation.

III.

LEGAL STANDARD

Federal Rule of Evidence 702 ("Rule 702") permits expert testimony from "[a] witness who is qualified as an expert by knowledge, skill, experience, training, or education," if: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

In examining the admissibility of experts, trial courts are tasked with a gatekeeper role, and should evaluate each proffered experts' opinions, methodology and reliability in determining whether the expert may testify. *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579, 113 S. Ct. 2786, 125 L. Ed. 2d 469 (1993) ("*Daubert*"). The objective of *Daubert*'s gatekeeping requirement is to ensure "that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999). The Court has broad discretion in determining whether the *Daubert* factors reasonably measure reliability in a given case. *Id.* at 153; *see also United States v. Hankey*, 203 F.3d

1160, 1168 (9th Cir. 2000).[5]

The key to admissibility is not the ultimate correctness of the opinions, but rather the process by which the expert came to the opinion. *Daubert*, 509 U.S. at 595. The court must "focus…solely on principles and methodology, not on the conclusions they generate". *Id.* In the absence of independent research or peer review, an expert must explain the process by which he or she reached the conclusions and identify some type of objective source demonstrating adherence to the scientific method. *In re Phenylpropanolamine Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1238 (citing *Daubert v. Merrell Dow Pharmaceuticals*, 43 F.3d 1311, 1318-19 (9th Cir. 1995)) ("*Daubert II")*; *see also, Domingo v. T.K.*, 289 F.3d 600, 605-06 (9th Cir. 2002). "Nothing in the text of [Rule 702] establishes 'general acceptance' as an absolute prerequisite to admissibility." *Daubert, supra,* at 589. "Shaky but admissible evidence is to be attacked by cross examination, contrary evidence, and attention to the burden of proof, not exclusion." *Primiano v. Cook*, 2010 U.S. App. LEXIS 8859 at *11 (9th Cir. 2010) (citing *Daubert* at 596). Further, scientific testimony may be admissible even if the opinions have not been subjected to peer review and publication. *Clausen v. M/V New Carissa*, 339 F.3d 1049, 1056 (9th Cir. 2003). The "trial court not only has broad latitude in determining whether an expert's testimony is reliable, but also in deciding how to determine the testimony's reliability." *Mukhtar v. Cal. State Univ.*, 299 F.3d 1053, 1064 (9th Cir. 2002) (citing *Hankey, supra*, 203 F.3d at 1167)

However, the admissibility standard under *Daubert* was intended to be a "liberal" one. *Zaprala v. USI Servs. Gp. Inc.*, 2013 WL 11483335 at *6 (E.D. Pa.

---

[5] Plaintiffs note that although Defendants rely heavily on a recent en banc 9th Circuit decision, *Estate of Barabin v. AstenJohnson, Inc.* 740 F.3d 457 (9th Cir. 2014), the *Barabin* court found that the trial court had not discharged its gatekeeping role by failing to provide *any* rationale or reasoning in permitting the expert to testify at trial *after* previously excluding that same expert. *Id.* at 461-62.

Mar. 20, 2013). The court's gatekeeping function is particularly important to be exercised liberally "considering the aura of authority experts often exude, which can lead juries to give more weight to their testimony." *Mukhtar*, 299 F.3d at 1063-64. Exclusion of an expert's opinions is a drastic measure because "[v]igorous cross examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 596, 113 S.Ct. 2786; *see also* Federal Rule of Evidence 702 Advisory Committee Notes.

A. General Causation v. Specific Causation

Experts in any field are subject to gatekeeping review by the trial court. *Kumho, supra* at 152. In mass tort pharmaceutical litigation, causation experts fall into two categories: (1) general causation experts and (2) case specific experts. *see* Annotated Manual for Complex Litigation §23. "General, or 'generic' causation has been defined by courts to mean whether the substance at issue had the capacity to cause the harm alleged, while "individual causation" refers to whether a particular individual suffers from a particular ailment as a result of exposure to a substance." *In re Hanford Nuclear Reservation Litig. v. E. I. Dupont*, 292 F.3d 1124 (9th Cir. 2002) (citing *Bonner v. ISP Technologies, Inc.*, 259 F.3d 924, 928 (8th Cir. 2001); *Sterling v. Velsicol Chem. Corp.*, 855 F.2d 1188, 1200 (6th Cir. 1988)).[6] In other words, "[g]eneral causation is concerned with whether an agent increases the incidence of disease in a group and not whether the agent caused any given individual's disease." Michael D. Green et al., *Reference Guide on Epidemiology*, in Reference Manual on Scientific Evidence 392 (Federal Judicial Center, 2d ed.

[6] Plaintiffs note that Defendants' motion, in accordance with the scheduling report, is limited to Dr. Bal's *general* causation opinions, i.e. that Nexium can cause osteoporotic-related injuries in the general population. Plaintiffs expect that Defendants will file case-specific causation motions at a later date at the discretion and direction of the Court.

2000). Usually plaintiffs in any given complex pharmaceutical litigation, *e.g.* Multidistrict Litigation, must establish general causation prior to offering causation opinions as to specific plaintiffs.

IV.

ARGUMENT

A. Dr. Bal is Exceptionally Qualified

Dr. Bal is an orthopedic surgeon, with over 25 years of experience. *See* Dr. Bal CV (Exhibit H). He has treated patients with osteoporosis, osteopenia and osteoporotic fractures, and presently does so (*see* Bal Dep. 88:23-25). Further, he has treated patients who have taken proton-pump inhibitors such as Nexium, in the course of his clinical practice, and continues to do so at present. (*see* Bal Dep. 70:3-10). In treating fractures at a Level-1 university-based trauma center, and in performing major reconstructive surgery on the long bones of the lower limbs, Dr. Bal has exceptional familiarity and expertise with the anatomy, physiology, and biomechanical properties of bone, both osteoporotic, and non-osteoporotic. Dr. Bal has offered the validly-formed and reliable opinion that Nexium, a PPI, can cause osteoporosis, osteopenia, and osteoporotic fractures in the general population.

In forming this opinion, Dr. Bal relied on his specialized knowledge, training and experience as a medical practitioner and orthopedic surgeon. Further, Dr. Bal did independent research and reviewed the relevant medical literature. (Bal Dep. 11:12-23). Dr. Bal did not rely on any Nexium plaintiff or plaintiffs' counsel in forming his opinions (Bal Dep. 14:20-25). Defendants' arguments that Dr. Bal is not qualified merely because he is not an epidemiologist or endocrinologist are in direct contrast to numerous district court opinions, including this District, finding specialized physicians—who were *not epidemiologists*—entirely qualified to offer opinions on causation. *see, e.g. Stanley v. Novartis Pharms. Corp.,* 2014 U.S. Dist. LEXIS 48499 at *22-23 (C.D. Cal. Apr. 2, 2014) (finding expert dentist qualified to testify); *In re Avandia Mktg.*, 2011 U.S. Dist. LEXIS 479 at *28-29 (E.D. Pa. Jan. 3,

2011) (finding expert dentist qualified to offer opinions based on epidemiological research); *Tucker v. SmithKline Beecham Corp*., 701 F. Supp. 2d 1040, 1047 (S.D. Ind. 2010) (finding expert psychiatrist qualified to testify on causation of anti-depressant medication).

1. Dr. Bal's testimony in *Fosamax* is irrelevant to his opinions in this litigation

Defendants attempt to argue that Dr. Bal's testimony in the *Fosamax* litigation refutes his opinions in this litigation. Their arguments and out-of-context citations could not be more misplaced or misleading. In this litigation, as noted *supra*, Dr. Bal has offered opinions that Nexium causes osteoporosis and osteoporotic-related fractures by inhibiting the calcium uptake in the digestive tract (*see* Bal Dep. Exhibit 3). Numerous peer-reviewed reports in the literature are on point in terms of supporting this exact mechanism whereby Nexium decreases acidity in the digestive tract (which is the desired benefit of the drug in treating heartburn), and as a side-effect, decreased acidity leads to poor calcium intake from the digestive tract (an undesirable side-effect that leads to calcium-poor, or osteoporotic bone that is prone to fracture). In contrast, in the *Fosamax* litigation, Dr. Bal has testified that Fosamax ***increases*** the calcium in certain areas of the femur, a contention that is well-supported by numerous peer-reviewed reports, and is in fact the mechanism whereby Fosamax exerts its desired and expected pharmacotherapeutic effect that is well-documented in the literature.[7] In each litigation, Dr. Bal has properly explained the methodology for his respective opinions.[8] The drugs are entirely distinct; Fosamax is used to treat osteoporosis by inhibiting the rate of calcium

---

[7] As Defendants here have acknowledged, Dr. Bal has testified for the defendants in the *Fosamax* litigation. His opinions in *Fosamax* acknowledge the mechanism of injury, but refute plaintiffs' experts' opinions as to whether Fosamax can actually cause femur fractures.

[8] Note that no Fosamax court has excluded Dr. Bal's opinions.

dissolution, thereby strengthening bone and reducing the risk of fracture, whereas a side-effect of Nexium is that reduced acidity in the digestive tract leads to less calcium intake which increases the risk of osteoporosis; these mechanisms have solid support in the scientific literature. For instance, consistent with the view of multiple peer-reviewed publications, Dr. Bal testified that Nexium compromises calcium intake, which is a well-recognized, and independent factor that worsens osteoporosis/risk of fracture (Bal Dep. 35:20-36:9). Dr. Bal acknowledged that calcium deficiency is not the only agent that can cause osteoporosis (Bal Dep. 37:18-25).

Further, Defendants' statement that Dr. Bal, when asked at his deposition in *Fosamax*, could not think of Nexium as a potential cause for osteoporosis is wholly misguided. Rather, Dr. Bal testified:

> Q: …Doctor, you mentioned certain drugs as risk factors [for osteoporosis]. Which drugs are you referring to?
>
> A: What I meant was alcohol, use of tobacco…
>
> …
>
> ***By no means is that an exhaustive list.***
>
> Q: Okay. Can you tell me some of the other ones, Doctor, that…you're coming to there [sic] that are risk factors for osteoporosis, the development of osteoporosis?
>
> A: Can't think of them right now.

(*see* Fosamax Dep. at pg. 80:5-21)(Griffin Decl., Exhibit I)(emphasis added).

It should be noted that Dr. Bal was giving opinions with focus to a particular **Fosamax** plaintiff. As a qualified expert giving precise opinions that related to a particular plaintiff allegedly injured by the drug Fosamax, and to the peculiar facts pertaining to that particular plaintiff, Dr. Bal prepared for the specific deposition. Further, the focus of the *Fosamax* deposition was on the factual circumstances of bilateral femur fractures, and the mechanism of injury specific to the plaintiff's Fosamax treatment. It is prejudicial for Defendants or the Court to expect Dr. Bal

(or any other expert) to recall at any moment specific facts from other cases he has testified in. In fact, Dr. Bal in his deposition in this case testified that he did not feel comfortable expressing particular opinions as to Fosamax because he had not prepared for that. (*see* Bal. Dep. 106:25-107:10; 110:13-111:2). Dr. Bal's hesitance to testify on matters outside the scope of the deposition he prepared for should not be used as a basis to claim he is not qualified to testify in the instant case.

B. Dr. Bal's Opinions are Reliable

Further, Dr. Bal has set forth reliable opinions, grounded in sound methodology and scientific rationale. *Daubert* set forth a non-exclusive list of factors for the court to consider, including: (1) whether the expert's theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4) whether the technique is generally accepted in the scientific community. *Id.* at 593-94. A "[c]ourt's gatekeeper role under *Daubert* is not intended to supplant the adversary system or the role of the jury." *In re Toyota Motor Corp. Unintended Acceleration Mktg., Sales Practices & Prods. Liab. Litig.*, 2013 U.S. Dist. LEXIS 154431 at *104 (C.D. Cal. Oct. 7, 2013) (citing *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003) (internal quotation marks and citation omitted). Here, Dr. Bal has offered reliable and scientifically-grounded opinions. Excluding them would improperly usurp the jury's role as the trier of fact.

1. The Mechanism of Injury of Nexium is a Class-Wide Effect

Dr. Bal opines that PPIs—a class of drugs which Nexium belongs to—interrupt calcium absorption in the gastrointestinal tract. (*See* Bal Dep. Exhibit 5). Dr. Bal's opinions are not inconsistent with valid expert testimony under *Daubert*, and Defendants' attempts to convince the Court otherwise should be disregarded. "Trained experts commonly extrapolate from existing data." *General Electric Co. v. Joiner*, 522 U.S. 136, 146, 118 S. Ct. 512, 139 L. Ed. 2d 508 (1997).

Recently, in a case involving Paxil, a selective serotonin reuptake inhibitor ("SSRI"), the defendant manufacturer made similar arguments to those Defendants present here. *see Tucker*, *supra*, 701 F. Supp. 2d 1040. There, the plaintiffs' expert, in a similar fashion to Dr. Bal in the instant case, formed opinions as to Paxil, a specific SSRI, based primarily (but not exclusively) on studies of ***all*** SSRI medications. In permitting the plaintiffs' expert to testify, the court noted "that Paxil is a unique chemical compound, but the court is not persuaded that [plaintiff's expert's] use of extrapolation or his reliance on data for SSRIs as a class renders his methodology in and of itself unreliable". *Id.* at 1056. Further, the court noted the significance of the FDA's regulations, specifically whether the FDA scrutinized Paxil itself or SSRIs as a class. The *Tucker* court emphasized that "although the FDA has recognized a variation in risk of suicidality amongst SSRIs, it has handled the drugs as a class". *Id.* The court here should adopt the same approach and reasoning. The FDA has treated Nexium and all other PPIs with the same level of scrutiny in risk-benefit assessment. *see* FDA Drug Safety Communication: "Possible increased risk of fractures of the hip, writs and spine with the use of **proton pump inhibitors**" (*see* Griffin Declaration, Exhibit J) (emphasis added). The FDA has concluded that the increased risk of fractures is a class wide effect of PPIs. *Id.* Dr. Bal's conclusions specific to Nexium, based in part on studies of PPIs as a class, are neither scientifically inconsistent nor inconsistent with *Daubert*'s admissibility standards.

2. Dr. Bal has Applied Accepted and Scientifically Reliable Methodology and Principles in Forming his Opinions

Dr. Bal has set forth well-founded opinions that there is a causal association between Nexium and OP. "Association" is “the degree of statistical dependence between two or more events or variables.” *In re TMI Litig*., 193 F.3d 613, 711 (3d Cir. 1999). Association is a term of art in epidemiology, and often defined as a relationship between two events "beyond what we would care to attribute to the play

of chance." *Id.* In forming his opinions, Dr. Bal looked at the overall epidemiology and observational studies and the weight of the overall evidence. (*see* Bal Dep. 35:5-14). Further, he reviewed the Food and Drug Administration's warnings and reports, scrutinized each study and made the appropriate considerations for each. *see generally,* Griffin Declaration, Exhibits A-F. Dr. Bal reviewed over thirty (30) studies and publications concerning the use of Nexium and other proton-pump inhibitors and the associated increased risk of osteoporotic-related injuries. Review of the peer-literature in professional journals is a scientifically-accepted, credible mechanism whereby scientific experts derive their opinion, and in the case of surgeons and physicians, use that information to make clinical decisions. Epidemiological and observational studies are useful in adding weight to an observation, particularly if such studies credibly and consistently point to a particular observation over time. Combined with accepted mechanisms of action, and corroborating evidence from other scientific studies, when combined with other supportive data, such studies can be used to imply causation, particularly when randomized clinical trials may be impossible to conduct. *Tucker, supra,* 701 F.Supp. 2d at 1060-61. While a particular epidemiological study or observational study may not be dispositive, an expert can rely on the weight of scientific evidence conferred by multiple, consistent epidemiological and observational studies to reach scientifically sound and credible conclusions. *Id.*

Further, Dr. Bal's opinions are supported by numerous observational studies that show a clear association between PPI use and increased fracture risk. In scientific studies, "increased risk" refers to a statistically significant difference in risk between groups being compared, e.g., between patients who take a drug versus a control group that does not take a drug. A statistically significant increase in risk of fracture, for example, refers to the likelihood that a result or relationship is caused by something other than mere random chance. *see* 3 David L. Faigman et al., *Modern Scientific Evidence* § 23:42 (2007). Thus, for example, a meta-analysis of

11 international studies showed a relationship between PPI use and increased fracture risk. *See* Griffin Declaration, Exhibit F. Other papers that have examined a large number of previously-published studies have concluded similarly, i.e., that PPI use is associated with an increased risk of hip and vertebral fractures. *See* Ngamruengphong, et al. *Proton Pump Inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies*, Am J Gastroenterology. (2011) 106(7): 1209-18 (Griffin Declaration, Exhibit K). A review article that summarized several studies examining PPI use and bone density reduction with increased fracture risk concluded that PPI use is associated with a modest increase in the risk of hip and vertebral fractures. *See* Lau, et al. *Fracture Risk and bone mineral density reduction associated with proton pump inhibitors.* Pharmacotherapy. 2012; 32(1): 67-79 (Griffin Declaration, Exhibit L). A large Canadian cohort of patients who were studied over a ten-year period also confirmed that PPI use increases the risk of fracture, even when other risk factors for fracture are scientifically controlled and accounted for. *See* Fraser, et al., *The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study,* Osteoporosis International. 2013; 24(4): 1161-8 (Griffin Declaration, Exhibit M).

The mechanism of action of PPI therapy includes interference with calcium absorption, which is known to increase fracture risk. *See* Ensrud, et al., *Low fractional calcium absorption increases the risk for hip fracture in women with low calcium intake*, Study of Osteoporotic Fractures Research Group. Ann Intern Med., 2000; 132(5): 345-53 (Griffin Declaration, Exhibit N). PPI drugs inhibit gastric acid secretion, which is thought to be necessary for calcium absorption by increasing the solubility of insoluble calcium salts. Impaired absorption of folate and vitamin B12 in PPI users, leading to alterations in homocysteine levels, has also been suggested as another mechanism contributing to the increased fracture risk. *See* McLean, et al., *Homocysteine as a predictive factor for hip fracture inolder persons,* New England Journal of Medicine; 2004; 350:2042-49 (Griffin Declaration, Exhibit O).

Finally, PPIs may exert a direct action on skeletal cells called osteoclasts. These cells are responsible for bone turnover, and are known to contain proton pumps that are inhibited by PPI therapy, leading to altered bone turnover. [Bal Dep. 163:18-22][9] While more than one mechanism may contribute to the increased risk of fracture, the most reasonable explanation seems to be that PPI drugs, such as Nexium, interrupt calcium absorption in the gastrointestinal system. As a result, the body has low calcium, leading to loss of bone mineral density, i.e., osteoporosis. Indeed, patients with osteoporosis are advised to use supplementary calcium in their diet. When low calcium leads to decreased bone mineral density and renders the diseased bone weak, an increased risk of fracture is manifest, in the distal radius, the pelvis and sacrum, the spine and the hip, exactly as the above-mentioned studies, and others published in the literature, have attested.

Collectively, the evidence is clear and Dr. Bal's opinions are consistent with that evidence that the use of PPI drugs, such as Nexium, is causally associated with an increased risk of fracture, particularly when these drugs are taken at prescription doses, for one year or longer. The weight of the evidence, including all epidemiological studies, observational studies, and mechanism of action, suggest a causal relationship (Bal Dep. 34:9-28). The most plausible reason for the increased risk of fracture is that PPI drugs decrease the uptake of calcium, leading to poor bone mineral density and weakened bones. Review of the existing peer-reviewed literature, and most importantly, review of the more recent studies that have been published in scientific journals, is entirely supportive of this position.

//

---

[9] *See also,* Mizunashi, et al., *Effect of omeprazole, an inhibitor of H+, K(+)-ATPase, on bone resorption in humans,* Calcif Tissue International, 1993; 53:21-5; Sheraly, et al., *Use of Gastrointestinal proton pump inhibitors to regulate osteoclastmediated resorption of calcium phosphate cements in vivo,* Curr Drug Deliv., 2009; 6:192-8.

3. Dr. Bal Does Not Make Generalized Opinions Regarding Nexium's Increased Risk of OP

Further, Dr. Bal acknowledged that some of the studies he used in forming his opinions had variables in the test groups (Bal Dep. 27:12-18). However, while he analyzed the impact of these variables, Defendants' experts overlook the variables and disregard the meaning of the studies (Bal Dep. 27:18-21). Defense experts make generalized opinions based on the presence of variables that studies do not show an association (Bal Dep. 29:15-30:17). Defendants' experts seem to require a "black and white" or "gold standard" study to support any inference of causal relationship. (Bal Dep. 32:17-33:2). Importantly, Dr. Bal reviewed newer studies which attempted to control the variables; these studies ***still showed*** the causal association between Nexium/PPI use and OP. (Bal Dep.27:22-28:5); *see also* Fraser, et al. (Griffin Declaration, Exhibit M).

Further, Dr. Bal puts limitations on his opinions, e.g. dose and duration requirements (Bal Dep. 39:11-19). He does not opine that Nexium causes OP at any dose and any duration of use, as Defendants' motion would represent he does. Nor does he opine that Nexium, or any other PPI, can cause *every* adverse bone-related injury, because the weight of the evidence does not suggest so[10] Specifically, in fact, Dr. Bal testified that Nexium (and other PPIs) was not associated with an increased risk of *all* fractures because the studies do not support that evidence. (*see* Bal Dep. 228:10-13). Dr. Bal limits his opinions as to the risk of fractures to

---

[10] Relying on the totality of evidence, Dr. Bal has testified that Nexium/PPIs do not cause bone spurs (*see* Bal Dep. 226:5-9; Nexium/PPIs do not cause osteopetrosis (*see* Bal Dep. 227:5-7); Nexium/PPIs do not cause an increased risk of bulging discs (*see* Bal Dep. 227:8-10); Nexium/PPIs do not cause an increased risk of carpal tunnel syndrome (*see* Bal Dep. 227:12-15); Nexium/PPIs do not cause an increased risk of degenerative arthritis or degenerative spondylosis (*see* Bal Dep. 227:22-25; Nexium/PPIs do not cause an increased risk of jaw fractures (*see* Bal Dep. 228:5-7); Nexium/PPIs do not increase the risk of finger or toe fractures (*see* Bal Dep. 14-16).

"locations of insufficiency fractures" which are supported by the studies. *Id.*

4. Dr. Bal's Methodology Meets the Bradford Hill Criteria

Post-*Daubert* courts analyzing the admissibility of expert opinions in exposure causation (e.g. pharmaceutical drugs) have implemented an assessment known as the Bradford Hill standard.[11] *See, e.g. In re Avandia Mktg., supra*; *Monroe v. Zimmer US Inc.*, 766 F. Supp. 2d 1012 (E.D. Cal. Feb. 11, 2011). Although Dr. Bal does not expressly refer to Bradford Hill (by name), his methodology parallels those in the Bradford Hill criteria[12], including the temporal relationship between Nexium and osteoporotic-related injuries (Bal Dep. 30:23-25), the weight of the evidence as a whole (Bal Dep. 35:1-14; 83:6-13), the strength of the association between Nexium use and osteoporotic-related injuries (Bal Dep. 39:20-40:6), alternative explanations for the association, the consistency with other scientific knowledge, and the biological plausibility of the mechanism of action of Nexium (Bal Dep. 73:8-13).

"Daubert did not set a threshold level of statistical significance either for admissibility or for sufficiency of scientific evidence." See Reference Manual on Scientific Evidence at 359-60, ftn.73 (Fed. Judicial Ctr. 2000) (quoting *Developments in the Law -- Confronting the New Challenges of Scientific Evidence*, 108 Harv. L. Rev. 1481, 1535-36 (1995)).

> The bottom line is the observational studies show an association repeatedly as a data tightens, the studies get better, the controls for confounding variables, the association between fracture risk and the use of PPI should

[11] The Bradford Hill criteria was developed by Sir Austin Bradford Hill in 1965 and presented to the Royal Society of Medicine. Since then, numerous courts have used the elements Bradford Hill set forth in evaluating the admissibility of causation opinions.

[12] It should be noted that although courts generally refer to these considerations as the "Bradford Hill *criteria*", an "expert need not consider or satisfy every criteria in order to support a causal inference" (*see In re Avandia Mktg.,* at *3).

> decrease if there was, in fact, confounding variables explaining the association. What you see is the opposite. The tighter the studies, this risk is still out there…

Bal. Dep. 143:1-10.

Dr. Bal's offered opinions were derived in a scientific method, with good grounds and appropriate validations supporting each opinion he has offered. *Daubert* at 590.

C. Defendants' Criticisms are Meritless, and Go to the Weight of Dr. Bal's Opinions, Rather than the Admissibility

1. Defendants' Experts Do Not Negate Dr. Bal's Reliable Opinions

In their motion, Defendants improperly contend that their own experts' opinions negate Dr. Bal's opinions simply because they are contrasting. As the 9th Circuit has previously explained (on numerous occasions), contrasting expert opinions go to the weight of the testimony, not the merits or admissibility. *Hangarter v. Provident Life & Accident Ins. Co.*, 373 F.3d 998, ftn. 14 (9th Cir 2004) (nature of expert's testimony went to the weight of the testimony, not the methodology). Defendants' experts rely primarily on the study by Dr. James Kaye and Dr. Hershel Jick ("Proton Pump Inhibitor Use and Risk of Hip Fractures in Patients without Major Risk Factors") (Exhibit 16 to Bal Dep.) This study was funded by AstraZeneca, the manufacture of Nexium, and Dr. Bal took that into account in weighing the study. (*see* Bal Dep. 255: 5-19).

In the Multidistrict Litigation involving Aredia® and Zometa®, the MDL court rejected arguments similar to those AstraZeneca and McKesson Corporation asserted here, namely that defense experts' opinions negated the plaintiffs' proffered experts' opinions. Permitting the plaintiffs' experts to offer expert testimony, the MDL court found that the arguments of both sides went to the weight of the respective experts, stating that "[d]efendant's arguments impugn the accuracy of Plaintiffs' experts' opinions but do not undermine the general scientific reliability

under Daubert." *In re Aredia & Zometa Prods. Liab. Litig.*, 2009 U.S. Dist. LEXIS 72034 at *5 (M.D. Tenn. Aug. 13, 2009).

2. Defendants' own experts admit that calcium deficiency can cause osteoporosis and fractures, consistent with the opinions offered by Dr. Bal

Even Defendants' own experts admit that Dr. Bal's opinion of the mechanism of injury, i.e. that decreased calcium can cause osteoporosis and other bone-related injuries, is scientifically accurate. [*see* Master Dkt. No. 256-5] Defendants' expert acknowledge that the mechanism of injury that Dr. Bal offers in his opinions is ground in scientifically-sound principles. In fact, Defendants' experts offer no opinion or evidence to refute that Nexium, or any other PPI, can cause a decrease in calcium uptake. Instead of examining the totality of evidence, Defendants' experts cherry-pick through selected epidemiological studies, or play down the risk of osteoporosis-induced fractures in patients taking Nexium, on the grounds that the merits of the drug in reducing acid reflux disease probably outweigh the fracture risk, at least when viewed on a population-wide basis.

3. Dr. Bal is Not Required to Prove the Mechanism of Injury is Generally Accepted in the Medical Community

Defendants argue that because Dr. Bal's opinions are allegedly not accepted by the medical community that they are inadmissible. Even if his opinions were not generally accepted—which they are[13]—this argument would be misplaced. The evidence that a particular opinion is or is not generally accepted by the medical community goes to the weight of the evidence, not the admissibility [cite]. Further, causation can be established even when the causal mechanism is unknown or not "black and white".

[13] *See generally,* Griffin Declaration, Exhibits A-F.

> Particularly in toxic tort cases, proving causation raises numerous complicated issues because the mechanisms that cause certain diseases and defects are not fully understood. Consequently, the proof of causation may differ from that offered in the traditional tort case in which the plaintiff details and explains the chain of events that produced the injury in question. In toxic tort cases in which the causal mechanism is unknown, establishing causation means providing scientific evidence from which an inference of cause and effect may be drawn.

Margaret Berger, The Supreme Court's Trilogy on the Admissibility of Expert Testimony, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 32 (Federal Judicial Center, 2d ed. 2000).

"The fact that the mechanism remains unclear does not call the reliability of the opinion into question." *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003) (citing *Daubert*, 43 F.3d 1311 (9th Cir. 1995)).

4. It Is The Jury's Responsibility to Weigh Both Parties' Expert Opinions and Decipher Good Data vs. Speculation

"Rule 702 d[oes] not require, or even permit, the district court to choose between…two studies at the gatekeeping stage. Both [parties'] experts [are] entitled to present their views, and the merits and demerits of each study can be explored at trial…Our system relies on cross-examination to alert the jury to the difference between good data and speculation." *Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 432 (7th Cir. 2013).

D. If the Court is Inclined to Grant Defendants' Motion, Plaintiffs Respectfully Request a *Daubert* Hearing

Should the Court, based on the papers and supporting evidence, still be inclined to grant Defendants' motion, Plaintiffs respectfully request that the Court permit an evidentiary hearing of Dr. Bal and the Defendants' offered experts.

Although courts are not required to hold evidentiary hearings under *Daubert*, the 9th Circuit has encouraged the use of evidentiary hearings in order to assist the court and provide both parties the opportunity to fully examine the proffered experts. *see In re Hanford Nuclear Reservation Litig. v. E. I. Dupont,* 292 F.3d 1124, 1138-1139 (9th Cir. 2002).

V.

CONCLUSION

As detailed above, Dr. Bal has offered opinions on Nexium's causal relationship to osteoporotic-related injuries and fractures, and his opinions are founded in reliable, scientifically-ground principles, meeting the standards required under Rule 702 and *Daubert*. Accordingly, Plaintiffs respectfully request that Defendants' motion be denied in its entirety.

DATED: May 5, 2014

Respectfully submitted,

GIRARDI | KEESE

By: */s/ Keith D. Griffin*

THOMAS V. GIRARDI
KEITH D. GRIFFIN
1126 Wilshire Boulevard
Los Angeles, CA 90017
Tel: (213) 977-0211
Fax: (213) 481-1554

Attorneys for Plaintiffs